NOVEL ACETOPHENONE OXIME DERIVATIVES

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3 Claims

ABSTRACT OF THE DISCLOSURE

The novel compounds of the Formula 1 were found to have strong anti-inflammatory and good analgesic activities. The compounds have a very low toxicity and produce substantially no adverse effects on the gastric wall. The compounds may be used to treat rheumatic affections.

The new compounds may be prepared and formulated by known methods.

The invention relates to novel acetophenone oxime derivatives of the General Formula 1 (see formulae). In this formula Hal indicates a chlorine or bromine atom, whilst R is a hydrogen atom or a group in which R₂ denotes a hydrogen atom, an alkyl group or an alkoxy group containing from 1 to 11 carbon atoms, or a group of the Formula 2, in which formula Hal' denotes a chlorine or bromine atom.

FORMULAE

The compounds of the Formula 1 were found to have a strong anti-inflammatory activity. The compounds have a very low toxicity, whilst they have substantially no adverse effect on the gastric wall. They furthermore have a good analgesic activity.

The compounds may be used in the treatment of rheumatoid arthritis, Bechterev's disease, arthritis psoriatica, collagen disease, serious osteoarthritis, acute gout, hemato-vascular periartthritis, acute sterile non-infected bursitis, thrombophlebitis and polyarthritis rheumatica acuta, and the like.

The dosage in which and the frequency at which the compounds are administered depend upon the nature and the seriousness of the affections in the treatment of which they are used. In general the amount to be daily administered will be from 50 to 1000 mg. As a rule from 100 to 500 mg. daily will be sufficient.

The analgesic effect of the compounds was determined in the carrageenin test which is carried out according to a modification of the method of Winter, Risley and Nuss, "Proc. Soc. Exp. Biol.," 111, 544 (1963). The compounds to be tested were suspended in a 1 percent by weight solution of tragacanth in water and orally administered to male rats (weight about 220 g.) which were made to fast for the 16 hours preceding the test. The administration of the substance was immediately followed by a water loading of 5 ml. One hour afterwards 0.05 ml of a 1.5 percent by weight carrageenin solution was intraplantarly injected and the thickness of the foot (dorsal-plantar distance) was determined with a micrometer.

Three hours after administration of the carrageenin the thickness of the resulting edema was determined. The swelling of the foot was expressed as a percentage of the 0 hour value. The percentage of the inhibition, which is a measure of the anti-inflammatory activity, was calculated according to the relation:

\[ \text{Percent of controls} - \text{percent of test animals} \times 100 \%
\]

From the results of a series of dosages an ED₅₀ value is computed, i.e. the dosage which gives a 50 percent reduction of the swelling.

The analgesic effect was determined by a modification of the method of Randall and Schlie ("Arch. Int. Pharmacodyn.," 109 409 (1957)). The reduction of the pain response due to increasing pressure on a yeast-inflamed rat foot is used as the criterion for the analgesic activity.

The test is carried out on male rats having weights between 100 g. and 300 g. One hour before the administration of the test compound the animals are given an intraperitoneal injection of 0.1 ml. of a 20% yeast suspension. The compounds to be tested are suspended in a 1% tragacanth solution and administered orally. One, two and four hours after administration of the test substance the pain threshold value with increasing pressure on the inflamed foot is measured. As a control the pain reaction of a group of animals not treated with a pharmacon was determined.

The results obtained are expressed as a percentage of the mean control value. From the results of a series of dosages an ED₅₀ value is calculated, i.e. the dosage which produced a 100% rise of the pain threshold.

The compounds according to the Formula 1 can be prepared by known methods.

Accordingly the invention relates to a method of producing novel acetophenone oxime derivatives which is characterized in that compounds of the Formula 1, where Hal represents a chlorine or a bromine atom and R is a hydrogen atom or a group

where \( R_1 \) is a hydrogen atom, an alkyl group or an alkoxy group containing from 1 to 11 carbon atoms or a group of the Formula 2, in which formula Hal' denotes a chlorine or a bromine atom, are prepared by methods which are known for preparing compounds of this type and by analogous methods.

For example, the compounds may be prepared by reacting a compound of the Formula 3 with a compound of the Formula 4, in which formulae the symbols have the aforementioned meanings. This reaction is preferably carried out in an inert solvent such, for example, as dimethylformamide, dimethysulfoxide, alcohols and the
The compounds may also be obtained by reacting a compound of the Formula 1, in which R represents a hydrogen atom or a metal atom, with a compound of the Formula 6, in which formule the symbols have the same meaning as in the Formula 1 and R₂ represents a halogen atom or a tosloxy group. When M represents a hydrogen atom an acid binder is preferably added. Otherwise the reaction conditions are equal to those of the aforementioned method.

The compounds may furthermore be prepared by reacting a compound of the Formula 7, where R₃ represents a halogen atom or a tosloxy group, with a compound of the Formula 8, in which R has the same meaning as in the Formula 1. This reaction is preferably carried out in the presence of a base. Lower alcohols may be used as solvents. The reaction is usually carried out at a temperature between 0° C. and 150° C.

The esters of the Formula 1 may alternatively be obtained by reacting an alcohol of the Formula 1 with a compound of the Formula 9, in which R₃ represents an OH-group, a halogen atom, an alkoxyl group containing from 1 to 4 carbon atoms or the group and R₄ has the same meaning as in the Formula 1, with the understanding that when R₄ represents a hydrogen atom R₄ is a halogen atom, an alkoxyl group or an OH-group. The reaction with compounds of the Formula 9, in which R₃ represents a halogen atom or an alkoxyl group, is preferably carried out under alkaline conditions, the other reactions under acid conditions. The reaction temperature as a rule lies between 0° C. and 150° C. Benzene, pyridine, dimethylformamide and the like may be used as solvents.

The solvents of the Formula 1 may also be prepared by reacting a compound of the Formula 5 (M=H) with ethylene oxide. The reaction is preferably carried out under basic conditions at temperatures between 20° C. and 80° C. Lower alcohols may be used as the solvents.

The compounds according to the invention may be worked up into pharmaceutical preparation such, for example, as tablets, pills, powders, injection liquids, ointments, suppositories, dragées and the like by known methods. Hence the invention also relates to the production of pharmaceutical preparations and to the preparations themselves. Suitable carrier material are the substances generally used for this purpose in pharmacy.

**EXAMPLES**

1. O-(2-hydroxymethyl)-4'-bromoacetophenone oxime—A solution of 2.27 g. of 2-(aminooxy)ethanol-HCl, 3.98 g. of 4'-bromoacetophenone and 4.92 g. of sodium acetate in 100 ml. of 80% ethanol was boiled under a reflux condenser for 5 hours. The solvent was distilled off in a vacuum and the residue was mixed with 100 ml. of water and 50 ml. of diethyl ether. The obtained layers were separated and the water layer was extracted twice with 50 ml. portions of diethyl ether. The collected ethereal extracts were washed twice with 50 ml. portions of water, then dried over anhydrous sodium sulfate and finally concentrated in a vacuum. The obtained concentrate was purified chromatographically on a silica gel column (eluant: benzene-ethylacetate 3:1) and then crystallized from petroleum ether containing 6% of benzene. After drying in a vacuum at 70° C. the supersubstance was obtained which had a melting point of 42°-44° C.

2. O-(2-bromoethyl)-4'-chloracetophenone oxime—A solution of 1.15 g. of sodium in 50 ml. of ethanol was mixed with 8.5 g. of 4'-chloracetophenone oxime. The solvent was distilled off in a vacuum at 40° C. and the residue was suspended in 35 ml. of N,N-dimethylformamide. This solution was mixed with 6.7 g. of 2-bromoethanol, after which the mixture was stirred at room temperature for 24 hours. Then the solvent was largely distilled off in a vacuum, the residue was mixed with 100 ml. of water and the mixture was extracted twice with 25 ml. portions of chloroform. The extract was dried over anhydrous sodium sulfate. The chloroform was distilled off and subsequently the residue was subjected to fractional distillation in a vacuum. The fraction having a boiling range from 154° C. to 162° C. and 0.7 mm. of mercury was purified chromatographically on a silica gel column using benzene/ethylacetate 3:1 as the eluant. The substance was crystallized from benzene/petroleum ether 1:25. Melting point 41°-42° C.

3. O-(2-hydroxyethyl)-4'-chloracetophenone oxime—A solution of 6.9 g. of sodium in 200 ml. of ethanol was mixed with 26.5 g. of 4'-chloracetophenone oxime and the resulting solution was added at room temperature whilst stirring to a mixture of 90 ml. of 1,2-dibromethane and 50 ml. of N,N-dimethylformamide. The mixture was heated to 65° C. and maintained at this temperature for 16 hours. After the precipitate formed had been drawn off, the solvent was largely distilled off in a vacuum, the residue was mixed with 200 ml. of water and the mixture was extracted twice with portions of 100 ml. of chloroform. After the extract had been dried over anhydrous sodium sulfate it was concentrated by evaporation in a vacuum and then distilled at a pressure of 0.015 mm. of mercury. The distillate was converted by reacting it in a solution of sodium hydroxide in 50% ethanol for about 30 hours. The solvent was then largely distilled off in a vacuum and the residue was neutralized with acetic acid. After the addition of water the mixture was extracted twice with diethyl ether. The ethereal extracts were washed twice with small portions of water and then dried over anhydrous sodium sulfate. By fractional distillation, chromatographic purification and crystallization in the manner described in Example 2 the supersubstance was obtained in pure form. Melting point 41°-42° C.

4. O-(2-acetoxyethyl)-4'-chloracetophenone oxime—A solution of 4.27 g. of O-(2-hydroxyethyl)-4'-chloracetophenone oxime in 50 ml. of pyridine was added drop by drop with stirring at 60° C. to a solution of 1.7 g. of acetylchloride in 30 ml. of benzene. After stirring for some hours at room temperature a solution of 0.5 acetylchloride in 20 ml. of benzene was added to the mixture, which was then stirred another hour. Then the solvent was distilled off in a vacuum and the residue was mixed with 100 ml. of water and 50 ml. of diethyl ether. The resulting layers were separated and the water layer was extracted with portions of 50 ml. of diethyl ether. The collected ethereal solutions were successively washed with 50 ml. water, two portions of 50 ml. of saturated sodium bicarbonate and again with 50 ml. of water. After the ethereal solution had been dried over anhydrous sodium sulfate it was concentrated by evaporation in a vacuum and the residue was distilled at a pressure of 0.7 mm. of mercury. The O-(2-acetoxyethyl)-4'-chloracetophenone oxime was obtained as a colorless oil having a boiling point of 132°-134° C. at a pressure of 0.7 mm. of mercury.

The following substances were synthesized in similar manners:

5. O-(2-(methoxyacryloxy)ethyl)-4'-chloracetophenone oxime—Melting point after crystallization from Petroleum ether 55°-56° C.

6. O-(2-(2,2,2-trimethylacetoxo)ethyl)-4'-chloracetophenone oxime—Boiling point 144°-146° C. at 0.8 mm. of mercury.
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(7) 2-[(4-chloro-a-methylbenzylidene)amino]oxy} ethylester of 2-[(4-chloro-a-methylbenzylidene)amino] oxy)acetic acid.—Oil.
(8) O-(2-octanoyloxy)ethyl] - 4' - chloroacetophenone oxide.—Oil.
(9) O - (2 - hydroxyethyl)-4'-chloroacetophenone oxide.—A solution of 4.9 g. of lithium in 400 ml. of methanol was diluted with 1.15 l. of absolute ethanol. 322 g. of 4'-chloroacetophenone oxide was added and the resulting clear solution was heated to 60° C. At this temperature 140 g. of ethylene oxide was passed into the solution with stirring for 1.5 hours. After the reaction mixture had been stirred for another hour it was mixed with 50 ml. of acetic acid and the solvents were distilled off in a vacuum. The residue was mixed with 1 l. of water and 1 l. of diethylether and the obtained layers were separated. The aqueous layer was washed once with 500 ml. of diethylether and then the collected ethereal extracts were washed twice with portions of 300 ml. water and then dried over anhydrous sodium sulfate. After removal of the ether by distillation the residue was subjected to fractional distillation in a vacuum. The fraction having a boiling range from 154° C. to 162° C. at 0.77 mm. of mercury was chromatographically purified on a silica gel column with a benzene-ethylacetate mixture (3:1) as the eluant. The substance obtained was crystallized from petroleum ether containing 4% of benzene and melted at 41-42° C.
Tablet.—200 g. of O-(2-hydroxyethyl)-4'-bromoacetophenone oxide was mixed with 190 g. of sec. calcium phosphate, 90 g. of microcrystalline cellulose and 120 g. of mixture comprising 200 parts of maize starch, 32 parts of talc and 4 parts of magnesium stearate until a homogeneous mixture had been obtained. From this mixture tablets each having a diameter of 13 mm. and a weight of 600 mg. were struck.
Suppository.—100 mg. of O-(2-hydroxyethyl)-4'-chloroacetophenone oxide was formed into a suppository with 1.5 g. of suppository material.
What is claimed is:
1. A compound of the formula
\[
\begin{array}{c}
\text{Hal} \\
\text{C}=\text{N}-\text{O}-\text{CH}_2\text{-CH}_2\text{-OH}
\end{array}
\]
in which Hal represents a chlorine or a bromine atom.
2. O-(2-hydroxyethyl)-4'-bromoacetophenone oxide.

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JOSEPH E. EVANS, Primary Examiner
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